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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

EXAMINER	

ART UNIT	PAPER NUMBER
	12

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 14 March 1997.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days~~, ~~whichever is longer,~~ from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 10-62 is/are pending in the application.

Of the above, claim(s) 45 is/are withdrawn from consideration.

☒ Claim(s) 10-28, 34-44, 62 is/are allowed.

☒ Claim(s) 29-33, 46-61 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 10-62 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 9

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

DETAILED ACTION

Response to Arguments

1. Claims 1-9 have been canceled and claims 10-62 have been added in the amendment of paper # 11, filed 14 March 1997. Claims 10-62 are pending in the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments filed 14 March 1997 have been fully considered but they are not deemed to be persuasive.

Election/Restriction

5. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 10-44 and 62, drawn to DNA encoding growth hormone receptor antagonists, cells transformed with said DNA, classified in at least class 435, subclasses 69.4 and 325, respectively, for example.

II. Claim 45, drawn to a transgenic animal, classified in class 800, subclass 2, for example.

III. Claims 46-61, drawn to gene therapy, classified in class 514, subclass 44, for example.

6. The inventions are distinct, each from the other because of the following reasons: Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not related because the Group I compositions are directed to DNA encoding the growth hormone receptor antagonist protein and Group II is directed to a transgenic animal. The inventions are physically and functionally distinct, as demonstrated by their separate classification.

7. Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the DNA of Group I could be used in an entirely different method rather than in the method of gene therapy of Group III, such as in a method of recombinant production of the growth hormone receptor antagonist protein..

8. Inventions II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not related because the invention of Group II is directed to an animal and the invention of Group III is directed to a method of gene therapy and are not disclosed as capable of use together. Furthermore, the inventions are physically and functionally distinct, as demonstrated by their separate classification.

9. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and the necessity for non-coextensive literature searches, restriction for examination purposes as indicated is proper.

10. Newly submitted claims 45-61 are directed to an invention that is independent or distinct from the invention originally claimed for the reasons given above.

Since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 45-61 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Incorporation by Reference

11. Applicant has attempted to incorporate essential material into the instant specification by reference to an allowed U.S. application (08/313,505). The matter which was to be entered at

page 7, line 29 of the specification is deemed to be essential since it forms the basis for newly added claim 61. Below are the guidelines for incorporation of essential material by reference (specific requirements are underlined). The incorporation by reference is improper because one or more of these conditions have not been met. At the present time, it cannot be determined if the issue fee for 08/313,505 has been paid. If Applicant has paid the issue fee in this application, the requirements under paragraphs 11 and 12 are the relevant requirements. Appropriate correction is required.

12. An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, Ex parte Schwarze, 151 USPQ 426 (Bd. App. 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent or (2) an allowed U.S. application in which the issue fee has been paid, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application. See *In re Fouche* , 439 F.2d 1237, 169 USPQ 429 (CCPA 1971).

13. Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure

required by 35 U.S.C. 112, first paragraph. *In re de Seversky* , 474 F.2d 671, 177 USPQ 144, (CCPA 1973). In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found.

14. If an application incorporates essential material by reference to a U.S. patent or a pending and commonly owned allowed U.S. application for which the issue fee has been paid, applicant may be required prior to examination to furnish the Office with a copy of the referenced material together with an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the copy consists of the same material incorporated by reference in the referencing application. However, if a copy of a printed U.S. patent is furnished, no affidavit or declaration is required.

15. If an application incorporates essential material by reference to a pending and commonly owned application other than one in which the issue fee has been paid, applicant will be required to amend the disclosure of the referencing application to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating the amendatory material consists of the same material incorporated by reference in the referencing application.

Abstract

16. Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art ***to which the invention pertains***.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

The abstract of the disclosure is objected to because it is not limited to the claimed invention. Language describing methods of treatment for other disorders for which the elected claims are not directed (i.e. transgenic animals) should not be included. Applicant's assertion that since the methods of treatment are claimed, that reference to these methods is included are not persuasive since the elected invention is directed to DNA. Correction is still required. See MPEP § 608.01(b).

Figures

17. The specification is still objected to for the Description of the Figures for the reasons of record, in part because the specification could not be amended and also because the appropriate corrections were not made. For example, at page 12, line 9, the specification recites "FIG. 4". This should be amended to recite "FIG. 4A-4C". Correction of the specification for Figures 4, 8 and 9 is still required.

Claim Rejections - 35 USC § 112

18. Claims 29-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 29 encompasses any DNA molecule which is 50% identical to a vertebrate growth hormone, has an amino acid substitution at amino acid which corresponds to Gly 119 of bovine growth hormone and encodes a protein having growth hormone antagonist activity. This claim is broader than the enabling disclosure and not commensurate in scope with the enabling disclosure because the structural limitations recited in the claim are not sufficient for meeting the functional limitation of the claim (i.e. encoding a protein having growth hormone antagonist activity). Growth hormone is a large protein (approximately 200 amino acids) and one of ordinary skill in the art would not reasonably expect a protein which is only 50% identical to the native protein to be able to functionally bind a receptor or retain any biological activity at all. Much is known about growth hormone, including that it possess two binding sites on the protein which binds two receptor "subunits" for receptor activation. In order for a protein to act as a receptor antagonist, there must be sufficient protein structure present to enable the protein to bind to the receptor and prevent the native protein from binding the receptor (i.e. acting as a competitive receptor antagonist). In the instant case, it would not be predictive which portions of the protein could be deleted or altered (up to 50%) and still obtain a protein which can function as a growth hormone

receptor antagonist. Furthermore, the claim does not require that the amino acid corresponding to Gly 119 of bovine growth hormone be present in the protein, and because this amino acid alteration is critical to the receptor antagonist activity, it would not be predictive that these molecules would possess the required activity. The other claims present in the instant application recite language similar to "is at least 50% identical with the sequence of a first reference vertebrate growth hormone, and differs therefrom solely in that". These claims provide guidance as to which amino acid substitutions can be made, which deletions can be made, and that the amino acid corresponding to Gly 119 of bovine growth hormone be present in the protein. These limitations are deemed to be necessary structural limitations which would provide the functional limitations which are recited in the claims.

In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

It is noted that assays are available for determination of growth hormone receptor antagonist activity, the standard for an enabling disclosure is not one of making and testing and the claims still constitute a "wish to know". Therefore, because these claims do not recite sufficient structural elements to meet the functional limitations of the claims, one of ordinary skill in the art would not be able to make and use the claimed invention without undue experimentation, absent clear and convincing evidence to the contrary.

19. Claims 29-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 recites "growth hormone antagonist activity", however, the metes and bounds of this claim cannot be determined by one of ordinary skill in the art. The instant specification describes growth hormone receptor antagonists, yet claims to antagonist activity are not limited to antagonism of the receptor. A compound which is an antagonist can have any opposing activity and is not limited to opposing activity at the receptor. Without the inclusion of the word "receptor", the skilled artisan would not be able to determine what type of antagonist activity is claimed and could therefore not ascertain the metes and bounds of the claims.

It is noted that Applicant asserts that "there is no reason to reject the new claims for lack of enablement or for indefiniteness" (see page 15 of response). However, it should also be noted that each application is examined on its own merits (*In re Hutchinson* 69 USPQ 138 (CCPA)).

CA 7/11/97

20. Claims 10-28 and 34-44 and 62 are allowable.

Rejoinder

21. Claims 10-28 and 34-44 are directed to an allowable product. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claims 46-61, directed to the process of making or using the patentable product, previously withdrawn from consideration as a result of a restriction requirement, are now subject to being rejoined. Process claims 46-61 are hereby rejoined and fully examined for patentability under 37 CFR 1.104 to 1.106. Claim 45, not directed to the process of making or using the patentable product, will not be rejoined.

Claim Rejections - 35 USC § 112

22. Claims 46-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification discloses a number of conditions which may or may not be caused or exacerbated by excess growth hormone receptor activity (see page 8 of the instant specification). However, the instant specification has not correlated the alleviation of any specific disease or disease symptoms by the administration of DNA encoding a growth hormone receptor

antagonist. Furthermore, the instant specification fails to provide even a single example of dosage amounts, dosage frequencies, or routes of administration of any DNA sequence encompassed by Applicant's claimed invention for the alleviation of any disease condition which may be associated with excess growth hormone receptor activity. The state of the prior art is such that gene therapy (which the claims encompass) is unpredictable as indicated in the NIH Recommendations cited with this Office action. Based on the NIH Report, gene therapy or DNA therapy is unpredictable on its face. The report states that the transferred genes must be adequately expressed and the reproducible expression of genes to achieve a therapy in general has not been observed in the art (NIH Report, page 8, paragraph 2 and page 8, paragraph 5, lines 6-10). Furthermore, the NIH Report on gene therapy stated that "... clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol ..." and that "the precise approach needs to be asked in each instance ..." ("NIH Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy", Orkin et al., December 7, 1995, page 1, item 2 and page 6, paragraph 1, lines 1-3).

The specification fails to provide any examples of dosages which would be effective for treating a patient or for treating a condition to obtain the desired result; i.e. prevention of a condition such as diabetes, acromegaly, giantism, etc. The claims must recite sufficient elements and steps for achieving the claimed method; without knowing what amount to administer or how to administer it effectively, one of ordinary skill in the art would not be able to practice the

invention as claimed. (See *In re Colianni* (CCPA) 195 USPQ 150.) *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

> "Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

As demonstrated by the Report cited above, the art of gene therapy is not only extremely unpredictable but is considered ineffective ("clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol"). Without some degree of predictability, the amount of experimentation necessary to determine a method of gene therapy as claimed would be undue. See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. Appls, and Interf. 1986) and *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

In Ex parte Forman, 230 USPQ 546 (Bd. Pat. Appls, and Interf. 1986), the Board considered the issue of enablement in molecular biology. The Board held that the following factors should be considered to determine whether the claimed invention would require of the skilled artisan undue experimentation:

(a) quantity of experimentation necessary
(b) amount of direction or guidance presented
(c) presence or absence of working examples
(d) nature of the invention
(e) state of the prior art
(f) relative skill of those in the art
(g) predictability or unpredictability of the art and
(h) breadth of the claims.

The level of skill in the art of molecular biology is high, but the nature of the invention is not well characterized. Therefore, the state of the prior art is relatively silent to the invention that is claimed. Although working examples are not required, they are one of the factors that must be considered when determining enablement, especially in light of the lack of guidance in the specification and the nature of the invention, and the instant specification fails to provide even a single example of prevention of any disease condition. Finally, the NIH Report clearly establishes the unpredictability of gene therapy. For the reasons mentioned above, it would require undue experimentation to practice the claimed invention based on the disclosure in the instant application, absent clear and convincing evidence to the contrary.

23. Claim 61 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a transgenic mouse, comprising administering a DNA molecule encoding the growth hormone receptor antagonist of claim 10 operatively linked to a promoter to a mouse, which has not completed its growth, wherein expression of said DNA molecule results in mice of smaller skeletal size, does not reasonably provide enablement for a method as described in claim 61. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claim is broader than the enabling disclosure because the instant claim currently encompasses the administration of DNA to any animal at any time prior to the completion of growth, however the instant specification only provides guidance for creation of a transgenic mouse via microinjection (page 42). In the art of gene therapy and transgenic transformation, there is a significant difference between administration of a DNA molecule to a germ cell and the administration of a DNA molecule to a developed embryo or animal. In the first instance, a transgenic animal is created and in the second, a chimeric animal is created. Based on the disclosure of the instant specification, it is believed that the enabled method is a method of producing a transgenic mouse, comprising administering a DNA molecule encoding the growth hormone receptor antagonist of claim 10 operatively linked to a promoter to a mouse, which has not completed its growth, wherein expression of said DNA molecule results in mice of smaller skeletal size. For the reasons given above in the previous rejection, the instant claims are not enabled for a method of producing any nonhuman animal because the art of gene therapy and transgenic transformation is unpredictable and the specification only provides a single example (i.e. mice). Furthermore, the instant claim as currently drafted fails to recite sufficient elements to achieve the desired result (a nonhuman animal which is of smaller-than-normal size) and these elements have been reflected in the drafted claim (recited in the grounds of rejection).

24. Claims 46-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 46 recites "excessive growth hormone activity" and "polypeptide having growth hormone antagonist activity". As mentioned in a previous rejection the metes and bounds of these limitations cannot be determined by one of ordinary skill in the art. The instant specification describes growth hormone receptor antagonists as well as describing growth hormone activity which is mediated by the growth hormone receptor, yet claims to antagonist activity are not limited to antagonism of the receptor. A compound which is an antagonist can have any opposing activity and is not limited to opposing activity at the receptor. Without the inclusion of the word "receptor", the skilled artisan would not be able to determine what type of antagonist activity is claimed and could therefore not ascertain the metes and bounds of the claims.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of

the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 46 recites the broad recitation animal, and the claim also recites human which is the narrower statement of the range/limitation. Claims 46-61 are indefinite for this recitation.

25. Claims 47-49 and 51-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 47, 51 and 52 contain the phrase "the antagonist" for which there is no antecedent basis in the preceding claims, making the claims indefinite and unclear. Claims 48-49 depend from these claims and are therefore, also indefinite.

26. Claim 61 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The limitation of "smaller-than-normal size" is unclear and indefinite because this could refer to weight, height, skeletal size, or any combination thereof. One of ordinary skill in the art would not be able to determine the metes and bounds of this claim (i.e. would a skinny animal qualify as "smaller-than-normal"?).

Conclusion

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Thursday from 8AM to 4PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached on (703) 308-2957. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**stephen.walsh@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Christine Saoud, Ph.D.
July 17, 1997
cA

JOHN ULM
PRIMARY EXAMINER
GROUP 1800